



UNITED STATES AIR FORCE RESEARCH LABORATORY

PROJECT RANCH HAND II

AN EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDES

REPRODUCTIVE OUTCOME UPDATE

JOEL E. MICHALEK
RICHARD A. ALBANESE
WILLIAM H. WOLFE

HUMAN EFFECTIVENESS DIRECTORATE
DIRECTED ENERGY BIOEFFECTS DIVISION
BIOMECHANISM AND MODELING BRANCH
2503 Gillingham Drive, Building 175E
Brooks Air Force Base TX 78235-5102

July 1998

Approved for public release; distribution is unlimited.

NOTICES

This report is published in the interest of scientific and technical information exchange and does not constitute approval or disapproval of its ideas or findings.

Using Government drawings, specifications, or other data included in this document for any purpose other than Government procurement does not in any way obligate the US Government. The fact that the Government formulated or supplied the drawings, specifications, or other data does not license the holder or any other person or corporation; or convey any rights or permission to manufacture, use, or sell any patented invention that may relate to them.

The Office of Public Affairs has reviewed this technical report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This technical report has been reviewed and is approved for publication.



JOEL E. MICHALEK, PhD
Project Scientist



RICHARD L. MILLER, PhD
Chief, Directed Energy Bioeffects Division

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE July 1998	3. REPORT TYPE AND DATES COVERED Final Report - 17 December 1984	
4. TITLE AND SUBTITLE Project Ranch Hand II: An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides - <u>Reproductive Outcome Update</u>			5. FUNDING NUMBERS PE - 65306F PR - 2767 TA - YA WU - 01	
6. AUTHOR(S) Joel E. Michalek Richard A. Albanese William H. Wolfe				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Air Force Research Laboratory Human Effectiveness Directorate Directed Energy Bioeffects Division Biomechanism and Modeling Branch 2503 Gillingham Drive, Building 175E Brooks Air Force Base TX 78235-5102			8. PERFORMING ORGANIZATION REPORT NUMBER AFRL-HE-BR-TR-1998-0073	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES This Technical Report was prepared for the Surgeon General, United States Air Force, 17 December 1984.				
12a. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution is unlimited.			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) Preliminary analyses of verified birth defects and neonatal deaths in Ranch Hand children are presented. Birth defects and neonatal deaths were reported by Ranch Hand and Comparison veterans at the baseline physical examination in the Air Force Health Study. At the time this report was prepared, negative responses to the birth defect and neonatal questions had not been completed. The change in the odds ratio relating birth defects and exposure group from before the father's service in Southeast Asia (odds ratio=0.73) to after the father's service in Southeast Asia (odds ratio=1.46) was statistically significant (p=0.024). The odds ratio relating neonatal death and exposure group also changed significantly (p=0.04) from before the father's service in Southeast Asia (odds ratio=1.00) to after the father's service in Southeast Asia (odds ratio=9.85).				
14. SUBJECT TERMS Birth defects Agent Orange Vietnam			15. NUMBER OF PAGES 39	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT UL	

RANCH HAND II UPDATED ANALYSIS OF LIVE BIRTH OUTCOMES

1. Introduction

Since the release of the baseline morbidity report in February 1984, birth defects and neonatal deaths reported by study participants during the baseline questionnaire have been verified by record review. This verification was accomplished by the review of birth and other medical records, birth certificates and death certificates. Verification of negative responses to the birth defect and neonatal death questions have not as yet been completed. Reported birth defects and neonatal deaths were labelled as belonging to one of nine verification result categories. Table 1 shows the number of reported birth defective children and neonatal deaths in each of the nine categories.

Table 1

VERIFICATION PROCESS SUMMARY AS OF 15 SEPTEMBER 1984
(Ranch Hand and All Comparisons)

<u>Verification Result</u>	<u>Number of Birth Defects</u>	<u>Number of Neonatal Deaths</u>
Cannot locate father	9	
Records unlocatable	46	8
No care sought	19	4
Refused delivery of records	31	4
Records destroyed	18	0
Confirmed	231	56
Not supported	23	0
Waiting for records	1	6

For the purpose of data analysis, these nine verification categories were collapsed to three for purposes of analysis, as defined in Table 2.

Table 2

VERIFICATION PROCESS COLLAPSED DEFINITIONS

<u>Verification Results</u>	<u>Analytic Category</u>
Cannot locate father	Unknown
Records unlocatable	Unknown
No care sought	Unknown
Refused delivery of records	Unknown
Records destroyed	Unknown
Confirmed	Yes
Not supported	No
Waiting for records	Unknown

The data analyzed in this report reflect the status of the verification process as of 15 September 1984. The date 15 September was chosen independently of the data and was dictated by the logistics of report preparation. An additional Ranch Hand child with Down's syndrome was identified but tour data for the father were unavailable at the time of analysis, and this child was omitted from these analyses.

2. Analytic Strategy

These analyses are directed at testing for the existence of a group by verified defect (or neonatal death) by time interaction. These data are categorized by group (Ranch Hand, Comparison) by verified birth defect (Yes, No) and by time of conception (Pre-Southeast Asia [Pre-SEA], Post-SEA). A description of a three-way group by defect by time interaction is best developed in terms of the odds ratio. The "odds" of a birth defect is a ratio of the probability of a defect to the probability of no defect. The ratio of this odds in the Ranch Hand group to the corresponding odds in the Comparison group is called the odds ratio. An odds ratio of unity indicates group equivalence as regarding birth defects. An odds ratio greater than unity is obtained when the

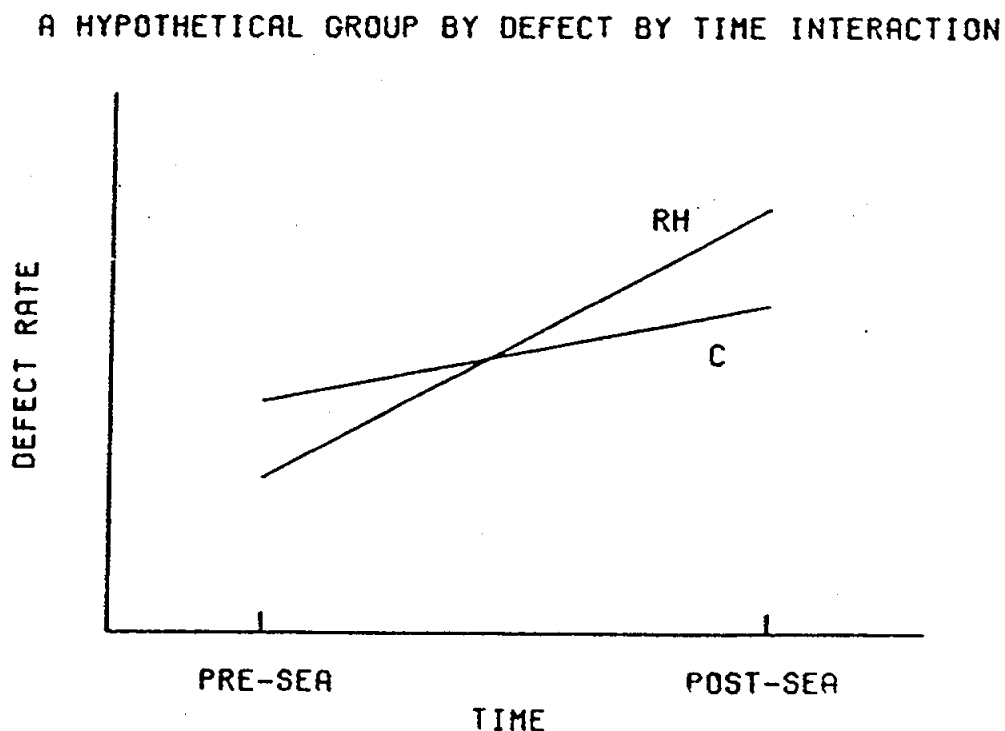
odds in the Ranch Hand group is greater than the odds in the Comparison group. The odds ratio thus summarizes the group by verified defect association. This odds ratio may, however, change with time of conception (pre-SEA, post-SEA). For example, an odds ratio of unity for pre-SEA conceptions and an odds ratio of two for post-SEA conceptions would be suggestive of a herbicide effect. A change in the odds ratio with time of conception indicates that the odds ratio is associated with time of conception. Such an association is termed a three-factor interaction by statisticians, the factors being group, verified birth defect and time of conception.

The preferred statistic in this report is the test of the hypothesis of no three-factor interaction. This hypothesis is equivalent to the statement that the odds ratio is constant with respect to time of conception; i.e., that the pre-SEA and post-SEA odds ratios are equal. A p-value for this test less than the nominal 0.05 would indicate the presence of a statistically significant three-factor interaction. In terms of the odds ratio, it would indicate that the pre-SEA and post-SEA odds ratios are significantly different. This test for no three-factor interaction is, in general, more appropriate than testing for group differences at each level of the third factor. More specifically, the test for equality of the pre-SEA and post-SEA odds ratios is entirely focused upon whether the odds ratio has changed with time, regardless of its pre-SEA value. Any test on post-SEA data only would assume that the pre-SEA birth experiences of both groups were equivalent, an assumption that appears unwarranted in these analyses since the matching variables, paternal age, race and military occupation are only weakly associated with the propensity to father birth defective children (Newcombe and Tavendale). These data suggest, in fact, that the Ranch Handlers and their matched Comparisons are nonequivalent groups with the Ranch Handlers having relatively fewer birth defective children

prior to service in Vietnam than do the Comparisons. The test for no three-factor interaction is, therefore, not only preferred but is the only analysis of these data that would account for a possible nonequivalence of these study groups prior to their Vietnam experience.

Consideration of a particular interaction pattern, one that actually obtains in these data, illustrates the effectiveness of these analyses; the pattern is shown in Figure 1.

Figure 1



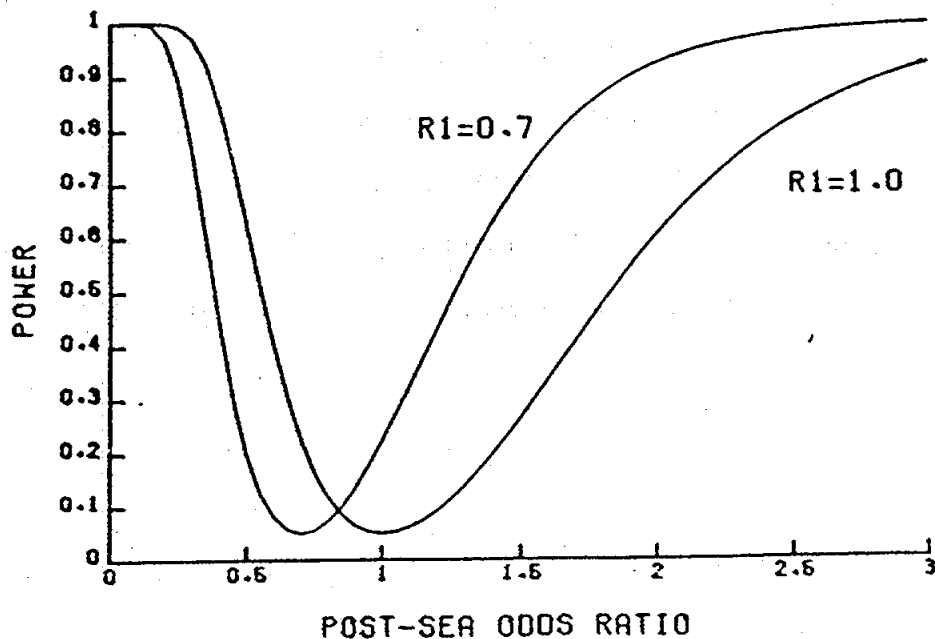
Here, both trend lines have a positive slope, as expected, by advancing paternal age but they cross over with the rates being different from each other, in one direction pre-SEA and in the opposite direction post-SEA. The

important point is not the crossover per se, since any significant group by defect by time interaction indicates that the lines differ. The important point concerns the pattern of switching rate differences; here the low-rate pre-SEA Ranch Handlers have overtaken the high-rate pre-SEA Comparisons. This pattern is reflected in these analyses by a pre-SEA odds ratio less than unity and a post-SEA odds ratio greater than unity.

The power of the test for no three-factor interaction is a function of the pre-SEA odds ratio, the post-SEA odds ratio, the numbers of Ranch Hand and Comparison conceptions pre-SEA and post-SEA, the number of defective births pre-SEA and post-SEA and the significance level. Two power curves are shown in Figure 2, for the 0.05 significance level and the marginal totals in Table 7, as a function of the post-SEA odds ratio for each of two values, 0.7 and 1.0, of the pre-SEA ratio.

Figure 2

POWER OF THE TEST FOR NO THREE FACTOR INTERACTION VERSUS
THE POST-SEA ODDS RATIO WHEN THE PRE-SEA ODDS RATIO(R_1)
EQUALS UNITY AND 0.7 AND MARGINAL TOTALS ARE THOSE OF TABLE 7



The graph corresponding to the pre-SEA odds ratio of 0.7 shows that the power of this test (given the data in Table 7) for detecting a change in the odds ratio from 0.7 to 1.5 is 70%. Thus, if the true pre and post-SEA odds ratios are 0.7 and 1.5, this test would correctly reject (at the 5% level of significance) the hypothesis of equal pre and post-SEA odds ratios in 70% of all repetitions of the study. While these power computations apply only to tables having the marginal totals of Table 7, they do serve to illustrate the statistical power characteristics of this study.

3. Analysis of Verified Birth Defects

A summary of the verification process, in terms of counts of children following the definitions in Table 2, is shown in Table 3. A child with multiple defects is counted only once in Table 3 and the subsequent analyses. For children with multiple verified defects, the most serious birth defect was analyzed. In Table 3 and elsewhere in this report, "original" Comparisons refer to those 1023 Comparisons who were asked to participate in the baseline physical examination before scheduling difficulties arose and "all" Comparisons refer to the entire cohort of 1660 matched Comparisons who received the baseline questionnaire. See Chapter V of the baseline morbidity report (Lathrop et al., 1984) for a full discussion of these groups. As in the baseline report, the primary analyses are those contrasting Ranch Hand children with original Comparison children. Contrasts of Ranch Hand and all Comparison children were, however, also carried out and are described throughout this report.

Table 3

CHILDREN WITH REPORTED BIRTH DEFECTS
AND VERIFICATION PROCESS RESULTS BY GROUP

<u>Group</u>	<u>Reported as Defective Verification</u>				<u>Unverified Negatives</u>	<u>Missing Data on Questionnaire</u>	<u>Total</u>
	<u>Yes</u>	<u>No</u>	<u>Unknown</u>	<u>Total</u>			
Ranch Hand	103	10	57	170	2479	13	2662
Original Comparison	85	7	43	135	2053	3	2191
All Comparisons	131	9	68	208	3156	13	3377

The 26 children with missing reported defect status on the questionnaire were not included in the verification process and they still carry a missing status. These 26 children with missing questionnaire data were deleted from all analyses. Seven children who were not categorized into one of the nine categories shown in Table 1 were included in the "unknown" verification status in the subsequent analyses. Two of these were children of original Comparisons and five were children of Ranch Handers. The total number of children in these tables ($2663 + 3377 = 6040$) corresponds to the total number of live births shown in Figure XI-1 of the baseline morbidity report.

Table 4 displays the verification status of reported birth defects by general category of the defect. The results of the verification process for specific defects by group and severity classification are contained in Appendix Table 1.

Table 4

ANALYZED BIRTH DEFECTS BY ORGAN OR SYSTEM
RANCH HAND AND ORIGINAL COMPARISONS ONLY

SEVERE

RANCH HAND								COMPARISON								
PRE-SEA				POST-SEA				PRE-SEA				POST-SEA				
Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable	Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable	ICD CODE	Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable	Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable
								NOMENCLATURE								
5	4		1	5	4	1		740-742 Nervous system	5	5						
13	8	1	4	10	1			744 Ear, face, neck	2		1	1				
1	1			2	9		1	745-747 Circulatory system	12	12			4	1		3
9	7		2	5	2			748 Respiratory system								
					3	1	1	749-750 Upper alimentary tract	7	5		2	5	4		1
3	2		1	1	1			751 Digestive	3	2	1					
8	5	1	2	2	2			752 Genital organs	1	1						
8	2		6	5	5			753 Urinary system	4	3		1				
								754-756 Musculoskeletal system	17	10	2	5	5	4		1
				1	1			757 Integumentary system					1	1		
1	1			2	2			758 Chromosomal	1			1	3	3		
2	2							759 Other & unspecified								
50	32	2	16	34	30	2	2		52	38	4	10	18	13		5

Table 4 (Cont'd)

ANALYZED BIRTH DEFECTS BY ORGAN OR SYSTEM
RANCH HAND AND ORIGINAL COMPARISONS ONLYMODERATE

RANCH HAND								COMPARISON									
PRE-SEA				POST-SEA				PRE-SEA				POST-SEA					
Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable	Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable	ICD CODE		Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable	Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable
								NOMENCLATURE									
3	1		2					743	Eye	1	1						
2	2			3		2	1	744	Ear, face, neck	1			1	1		1	
								745-747	Circulatory system	2	2			1	1		
								748	Respiratory system	1	1						
				1	1			749-750	Upper alimentary tract	1	1						
3			3					751	Digestive					1	1		
3			3	3	2		1	752	Genital organs	3	3			4	4		
1	1			1	1			753	Urinary system								
18	9	1	8	9	7	1	1	754-756	Musculoskeletal system	15	6	1	8	11	8	1	2
2	1		1	3	2	1		757	Integumentary system	2	1		1	1	1		
32	14	1	17	20	13	4	3			26	15	1	10	19	15	2	2

Table 4 (Cont'd)

ANALYZED BIRTH DEFECTS BY ORGAN OR SYSTEM
RANCH HAND AND ORIGINAL COMPARISONS ONLYLIMITED

RANCH HAND								COMPARISON								
PRE-SEA				POST-SEA				PRE-SEA				POST-SEA				
Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable	Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable	ICD CODE	Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable	Re-ported	Veri-fied	Not Sup-ported	Not Veri-fiable
								NOMENCLATURE								
1			1	2	2	1		740-742 Nervous system	1			1	1			1
				1				745-747 Circulatory system								
1			1	4	2		2	748 Respiratory system					1	1		
								749-750 Upper alimentary tract					1			1
3	1		2	9	4	1	4	751 Digestive	1			1				
								754-756 Musculoskeletal system					6	3		3
3	1		2	10	4	2	4	757 Integumentary system	7			7	2		1	1
8	2		6	26	12	4	10		9			9	11	4	1	6

As in the baseline report, only those verified birth defects satisfying the definition given in Appendix V of the baseline report are analyzed. Table 5 shows the counts of the children in Table 3 having verified birth defects within the definition by time of conception (pre-SEA, post-SEA), verification results (Yes, No, Unknown) and group (Ranch Hand, Original Comparison, All Comparisons). As previously noted, one Ranch Hand child with a verified confirmed birth defect could not be classified by time of conception because tour data for his father are missing.

Table 5
CHILDREN WITH MULTIPLE BIRTH DEFECTS

	Pre-SEA			Post-SEA		
	S	M	L	S	M	L
<u>Ranch Hand</u>						
Number of children	10	3	0	8	5	2
Number of conditions reported	22	8	0	13	16	8
Number of conditions verified	17	2	0	13	12	5
<u>Original Comparison</u>						
Number of children	7	1	0	3	5	0
Number of conditions reported	12	5	0	6	9	1
Number of conditions verified	10	2	0	6	7	0
<u>All Comparisons</u>						
Number of children	8	2	1	5	8	0
Number of conditions reported	14	8	1	11	15	2
Number of conditions verified	12	4	0	9	13	1

Table 5 shows the number of children in each group reported to have multiple birth defects and the verification status of these defects. If a child had defects with differing severity, the child was placed in the category of his/her most severe defect.

Table 6

CROSS TABULATION OF CHILDREN HAVING REPORTED BIRTH DEFECTS
SATISFYING THE DEFINITION

Group	Pre-SEA			Post-SEA			Totals	
	Yes	No	Unknown	Yes	No	Unknown	Pre-SEA	Post-SEA
Ranch Hand	47	2	41	56	9	15	90	80
Original Comparison	53	4	30	32	3	13	87	48
All Comparisons	73	5	45	58	4	22	123	84

The totals in Table 6, together with the Ranch Hand and all Comparison children with no time of conception information, are slightly different from those totals shown in Table XI-10 of the baseline report, because Table XI-10 contains data that were not analyzed in the baseline report. The counts in Table 6 do account for all children having reported birth defects within the definition and reflect minor numeric changes due to the verification process.

Following the format of the baseline report, these analyses are focused on the Ranch Handers and the original Comparisons. While these contrasts are of primary importance, corresponding Ranch Hand versus all Comparison contrasts are shown in the Appendix. The subject of these statistical investigations is the change, if any, in the group (Ranch Hand, Original Comparison) by verified birth defect relationship with respect to the time of conception as pre-SEA or post-SEA.

A statistical assessment of the Ranch Hand and original Comparison data with a dichotomous response (unknown, not unknown) did not reveal any significant difference in the pattern of verification between the groups ($p = 0.65$), adjusted for time of conception. The corresponding analysis of the Ranch Hand and all Comparison data gave a similar result ($p = 0.71$). Thus, patterns of

false positive reporting do not appear to differ between the groups. Since there is no association in these data between groups and "unknown" verification status, the children having unknown verification status have been removed from subsequent analyses. Verification of birth defects, therefore, has only two values (yes, no). These data, with unknowns removed, are summarized in Table 7.

Table 7

CHILDREN WITH VERIFIED BIRTH DEFECTS WITHIN THE DEFINITION
BY VERIFICATION OUTCOME, GROUP AND TIME

<u>Group</u>	<u>Pre-SEA (%)</u>		<u>Post-SEA (%)</u>	
	<u>Yes</u>	<u>No</u>	<u>Yes</u>	<u>No</u>
Ranch Hand	47 (2.8)	1630 (97.2)	56 (6.3)	838 (93.7)
Original Comparisons	53 (3.8)	1351 (96.2)	32 (4.4)	697 (95.6)

The p-value for the test of the hypothesis of no group by defect by time in these data is 0.024. This implies that the pre-SEA odds ratio for verified birth defects, 0.73, is significantly different from the post-SEA odds ratio, 1.46, for contrasting Ranch Handers and original Comparisons ($p = 0.024$). The equivalent analysis using the data from all Comparisons (Appendix Table 2) resulted in a similar finding ($p = 0.023$).

As reported in the baseline report, an analysis on reported defects, ignoring the verification results, shows a significant three-way reported defect by group by time interaction ($p = 0.047$), with odds ratios changing from 0.85 to 1.39.

Table XI-16 of the baseline report shows counts, but no analysis, of reported birth defective children by group (Ranch Hand, original Comparisons), by occupation (officer, enlisted flying, enlisted ground) and by time of conception. Table 8 shows the corresponding counts of children by birth defect verification outcome (yes, no).

Table 8

CHILDREN WITH VERIFIED BIRTH DEFECTS BY OCCUPATIONAL GROUP AND TIME

Occupation	Group	Pre-SEA (%)		Post-SEA (%)	
		Yes	No	Yes	No
Officer	Ranch Hand	24 (3.0)	774 (97.0)	9 (3.9)	221 (96.1)
	Original Comparisons	27 (3.9)	674 (96.1)	12 (5.3)	215 (94.7)
Flying	Ranch Hand	6 (1.7)	345 (98.3)	9 (8.7)	95 (91.3)
	Enlisted Original Comparisons	11 (3.5)	307 (96.5)	4 (3.8)	102 (96.2)
Ground	Ranch Hand	17 (3.2)	511 (96.8)	38 (6.8)	522 (93.2)
	Enlisted Original Comparisons	15 (3.9)	370 (96.1)	16 (4.0)	380 (96.0)

Log-linear analyses of the data in Table 8 show no significant four-way, group by defect by time by occupation, interaction ($p = 0.20$). This lack of four-way interaction allows consideration of a test for the three-way interaction of interest (defect by group by time) adjusted for occupation. This test gives a p -value of 0.061. These findings suggest that the pre-SEA odds ratio and post-SEA odds ratio are only borderline significantly different, when adjustment for occupation is performed. Similar analyses of the data from the total Comparison group revealed equivalent results (Appendix Table 3). Here, and elsewhere in this report, adjustments for covariates are carried out to reduce bias in the analysis. The price for this reduction, in the absence of more data, is a loss in precision. Hence, the slightly increased p -value of 0.061, as compared with the unadjusted value, 0.024, reflects either true absence of a three-way (defect by time by group) interaction or a reduced ability

to detect a true three-way interaction due to an increased number of cells with a fixed data base. A distinction between these two alternatives (a crude analysis with more potential bias and better power or a refined analysis with less bias but with lower power) can not be made without more data or more refined statistical procedures.

An analysis of the data in Table 7, adjusted for four covariates (mother's smoking and drinking during pregnancy, mother's age at conception and father's age at conception), was carried out. The three-way interaction (group by defect by time), adjusted for mother's smoking, drinking and age and father's age, is borderline statistically significant in the full analysis ($p = 0.072$). Equivalent statistical testing with the data from the total Comparison group resulted in similar findings ($p = 0.06$), and these results are shown in Appendix Table 4.

Table 9

CHILDREN WITH VERIFIED BIRTH DEFECTS
BY GROUP, TIME OF CONCEPTION AND VERIFICATION OUTCOME,
WITH BOTH PARENTS UNDER 35 AT CONCEPTION AND
MOTHERS WHO DID NOT DRINK ALCOHOL DURING PREGNANCY

A. Mothers not smoking during pregnancy.

<u>Group</u>	<u>Pre-SEA (%)</u>		<u>Post-SEA (%)</u>	
	<u>Yes</u>	<u>No</u>	<u>Yes</u>	<u>No</u>
Ranch Hand	25 (3.0)	818 (97.0)	28 (5.4)	493 (94.6)
Original Comparisons	24 (3.1)	742 (96.9)	20 (5.0)	380 (95.0)

B. Mothers smoking during pregnancy.

<u>Group</u>	<u>Pre-SEA (%)</u>		<u>Post-SEA (%)</u>	
	<u>Yes</u>	<u>No</u>	<u>Yes</u>	<u>No</u>
Ranch Hand	12 (3.1)	379 (96.9)	11 (8.1)	125 (91.9)
Original Comparisons	19 (6.3)	282 (93.7)	4 (3.3)	116 (96.7)

The fully adjusted analysis just described is subject to criticism because of the many empty cells in the full contingency table. In the above analyses, 2530 (60.6%) of the 4178 children of Ranch Handers and original Comparisons were offspring of mothers who did not drink or smoke during pregnancy and were under 35 at time of conception and of fathers who were under 35 at conception; 948 (22.7%) of these children had mothers who smoked and did not drink during pregnancy and were under 35 at time of conception and had fathers who were under 35 at conception. A summary of the data in these two categories of covariate values is shown in Table 9. Account of the structure of the full table would then be taken by separate analyses within each of the two arrays shown in Table 9. These analyses were accomplished. There is a significant four-way interaction in the data shown in Table 9 ($p = 0.051$), indicating that three-way interaction of interest (group by defect by time) changes with maternal smoking habits. The corresponding four-way interaction in the Ranch Hand versus all Comparison data was not significant, ($p = 0.13$). Analyses within parts A and B of Table 9 were then carried out. The three-way interaction (group by defect by time) is not significant in the data of part A of Table 9 (mother not smoking during pregnancy). However, this three-way interaction is statistically significant ($p = 0.012$) in the data of part B of Table 9 (mother smoking during pregnancy); the odds ratio changes from 0.47 to 2.55. In summary, there is an indication that smoking by the wife of a Ranch Hand during pregnancy is associated with a Ranch Hand versus Comparison differential in birth defects over time of conception ($p = 0.051$).

Counts of verified birth defective children by severity of defect (light, medium, severe), group (Ranch Hand, original Comparison) and time of conception (pre-SEA, post-SEA) are shown in Table 10. The definition of severity is taken from the baseline report and is shown below:

Severe: Conditions which are life threatening or produce severe handicaps (e.g., physical, mental, motor).

Moderate: Conditions which are not life threatening and handicaps which, with medical care, will not interfere with the individual's overall health or socioeconomic progress.

Limited: All conditions which, without medical care, would not interfere with the individual's health or socioeconomic progress.

Table 10

CHILDREN WITH VERIFIED BIRTH DEFECTS
BY SEVERITY, GROUP AND TIME OF CONCEPTION

<u>Time</u>	<u>Group</u>	<u>Defective</u>			<u>Not Defective</u>
		<u>Light</u>	<u>Moderate</u>	<u>Severe</u>	
Post-SEA	Ranch Hand	12	14	30	838
	Original Comparison	4	16	12	697
Pre-SEA	Ranch Hand	2	13	32	1630
	Original Comparison	1	15	37	1351

A log-linear analysis of the data in Table 10 revealed a borderline group by severity by time of conception interaction ($p = 0.08$). An analysis limited to the children with verified defects, categorized as light, moderate or severe, showed no statistically significant group by severity by time of conception interaction ($p = 0.29$). The corresponding analyses with all Comparisons also revealed no significant three-way interaction ($p = 0.13$ and $p = 0.64$, respectively). These results are displayed in Appendix Table 5.

Two data-dependent analyses (post hoc) were also conducted on the data in Table 10. First, children classified as having limited birth defects were reclassified as "not defective," leaving only two categories of defective children, moderate and severe, in the analysis. The results of this analysis revealed a statistically significant group by defect by time interaction ($p = 0.04$). Second, children classified as having limited or moderate birth defects were reclassified as "not defective," leaving only the severe category of defective children in the analysis. The results of this analysis revealed a statistically significant group by defect by time interaction ($p = 0.01$), with the odds ratio changing from 0.72 to 2.07. These analyses suggest that the three-way interaction found in Table 7 does not depend on severity of defect. The corresponding analyses were also carried out on all of the data, shown in Appendix Table 6; the results were similar, with the respective p -values being 0.09 and 0.04. These post hoc analyses are of secondary importance relative to the primary analyses shown elsewhere in this report.

Counts of verified birth defective Ranch Hand children conceived after the father's duty in Southeast Asia are shown in Table 11 according to their father's occupation (officer, flying enlisted, ground enlisted) and estimate of herbicide exposure (low, medium, high).

Table 11

CHILDREN WITH VERIFIED BIRTH DEFECTS
POST-SEA RANCH HAND BY FATHER'S OCCUPATION AND HERBICIDE EXPOSURE

Exposure	Officer (%)		Flying Enl (%)		Ground Enl (%)	
	Yes	No	Yes	No	Yes	No
Low	3 (4.0)	72 (96.0)	0 (0.0)	29 (100)	11 (1.6)	165 (98.4)
Medium	4 (7.1)	52 (92.9)	4 (12.5)	28 (87.5)	11 (4.9)	214 (95.1)
High	1 (1.2)	83 (98.8)	5 (11.4)	39 (88.6)	16 (10.3)	149 (89.7)

Statistical analyses of the data in Table 11 were restricted to the enlisted ground cohort due to low counts in the officer and flying enlisted data. Analyses within the ground enlisted cohort on the occurrence of birth defective children and herbicide exposure were carried out using each of the four covariates, one at a time. These four analyses are summarized in Table 12. No significant relationships between the occurrence of birth defective children and herbicide exposure, adjusted for these covariates, were seen in these data.

Table 12

EXPOSURE ANALYSIS BY CHILDREN WITH VERIFIED BIRTH DEFECT
(Ranch Hand Enlisted Ground Personnel Only)

Covariate	P-Values for	
	No Defect by Exposure by Covariate Interaction	No Defect by Exposure Interaction
Mother smoking	0.59	0.25
Mother drinking	0.89	0.20
Mother's age	0.35	0.24
Father's age	0.65	0.21

4. Neonatal Death Analysis

Verification of reported neonatal deaths was also accomplished during the same time period, and the data are summarized in Table 13.

Table 13

REPORTED NEONATAL DEATHS
AND VERIFICATION PROCESS RESULTS BY GROUP

<u>Group</u>	<u>Positive Responses</u>			<u>Negative Responses</u>	<u>Total</u>
	<u>Verified</u>	<u>Unverified</u>	<u>Total</u>		
Ranch Hand	31	9	40	2623	2663
Original Comparison	17	4	21	2170	2191

These data are shown in Table 14, by time of conception (pre-SEA, post-SEA), verified neonatal death (Yes, No) and group (Ranch Hand, Original Comparison).

Table 14

VERIFIED NEONATAL DEATHS BY TIME AND GROUP
(p = 0.0378)

<u>Group</u>	<u>Pre-SEA (%)</u>		<u>Post-SEA (%)</u>	
	<u>Yes</u>	<u>No</u>	<u>Yes</u>	<u>No</u>
Ranch Hand	18 (1.0)	1705 (99.0)	12 (1.3)	905 (98.7)
Original Comparison	15 (1.0)	1420 (99.0)	1 (0.3)	743 (99.7)

A log-linear analysis of the data in Table 14, unadjusted for other covariates, shows a significant three-way (group by time by neonatal death) interaction ($p = 0.04$). In other words, the pre-SEA odds ratio, 1.00, is significantly different from the post-SEA odds ratio of 9.85. A parallel analysis on verified data from all Comparisons gave similar results with a significant change ($p \leq 0.01$) in the odds ratio from 0.93 to 8.67. A corresponding analysis using unverified data from original Comparisons in the baseline morbidity report resulted in a borderline significant finding ($p = 0.09$), with the pre and post-SEA odds ratios being 1.23 and 3.83. When the unverified data from

the total Comparison group (originals plus replacements) were used in the baseline morbidity report, a statistically significant result was obtained ($p \leq 0.01$), with the pre and post-SEA odds ratios of 1.06 and 5.06.

The neonatal death data are too sparse to permit a meaningful analysis stratified on the exposure index or other covariates.

5. Conclusions

Birth defects and neonatal deaths reported by study participants during the administration of the questionnaire phase of the baseline study have been subjected to verification based upon birth/death certificates and medical records. The results of the verification process are summarized in the following two tables.

Table 15

VERIFICATION STATUS OF CHILDREN WITH REPORTED BIRTH DEFECTS BY GROUP

<u>Group</u>	<u>Number Reported</u>	<u>Records Obtained</u>	<u>Number Verified</u>	<u>Percent Verified</u>
Ranch Hand	171	118	103	60.6
Original Comparisons	135	101	85	63.0
All Comparisons	208	154	131	63.0

Table 16

VERIFICATION STATUS OF REPORTED NEONATAL DEATHS BY GROUP

<u>Group</u>	<u>Number Reported</u>	<u>Number Verified</u>	<u>Percent Verified</u>
Ranch Hand	40	31	77.5
Original Comparisons	20	16	80.0
All Comparisons	32	26	81.3

In spite of extensive efforts, some records were unobtainable and their receipt is not anticipated. The verification of positive reports of these conditions were not statistically different in the three groups. Thus, differential reporting of positive responses to the birth defect and neonatal death questions does not create a detectable bias in these data.

Statistical analyses comparable to the analyses on reported but unverified data in the baseline report were conducted, and similar findings were observed. There was an increase in the risk of Ranch Hand birth defects with time (pre versus post-Southeast Asia), and this change is statistically significant. These data were also stratified on the smoking history of the mother during the pregnancy in question. There were no group differences in birth defects among those women who did not smoke; however, there was a significant change in risk of birth defects with time among Ranch Hand children born to mothers who did smoke during pregnancy.

The herbicide exposure index was applied to these data, but the number of defects among the relatively small strata of officers and enlisted flyers made a meaningful analysis impossible. However, the larger group of ground enlisted personnel was large enough to permit this analysis. This analysis did not

reveal an association between herbicide exposure and the occurrence of birth defects. The exposure index used in this report is a theaterwide estimate of exposure and is not individual-specific and needs further refinement.

The neonatal death data were also reanalyzed. A significant change in risk of the occurrence of neonatal death with time was noted; however, this is due in part to an obvious decrease with time in neonatal deaths born to Comparisons' wives. The Ranch Hand rate was stable with time. These analyses were, however, unadjusted for maternal age at time of conception. Additional adjusted analyses will be carried in future updates or other socioeconomic variables of possible importance.

The reanalysis of these data corroborated the findings of the baseline report; however, once again, no consistent relationship to exposure was observed. The next step in the full analysis of these data is to verify the negative reports to complete the assessment of differential reporting. It is anticipated that another 12 months will be required to complete the collection of medical records on the more than 6000 live births reported by the study participants.

APPENDIX

Appendix Table 1

ANALYZED RANCH HAND

SEVERE

ICD CODE	PRE-SEA				NOMENCLATURE	POST-SEA			
	Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable		Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable
22801					Hemangioma of skin and subcutaneous tissue	1	1		
74100	2	2			Spina bifida with hydroce- phalus				
74190					Spina bifida without hydroce- phalus	2	2		
7423	2	2			Hydrocephalus				
74259	1			1	Other specified anomalies of spinal cord	1		1	
7429					Unspecified anomaly of brain, spinal cord	2	2		
74409					Absence of ear	1	1		
74511	1	1			Double outlet right ventricle	1	1		
7454	1			1	Ventricular septal defect				
7455					Atrial septal defect	2	1		1
7459	1			1	Unspecified defect of septal closure				
74602					Pulmonary valve stenosis	1	1		
74686	1			1	Congenital heart block				
74689					Other specified anomalies, heart	1	1		
7469	3	1	1	1	Unspecified anomaly of heart	2	2		
7470	1	1			Patent ductus arteriosus	3	3		
74721	1	1			Anomalies of aortic arch				
74722	1	1			Atresia & stenosis of aorta				
7473	3	3			Anomalies of pulmonary artery				
7485	1	1			Agenesis, hypoplasia, dyspla- sia of lung	2	2		
74900	2	2			Cleft palate	1	1		
74910	2	2			Cleft lip	2	1		1
74920	1	1			Cleft palate with cleft lip				
7503					Tracheoesophageal fistula	1	1		
7505	4	2		2	Pyloric stenosis	1		1	
7511	1			1	Atresia & stenosis of small intestine				
75161	1	1			Biliary atresia				
7519	1	1			Unspecified anomaly of diges- tive system	1	1		
7530	1	1			Renal agenesis & dysgenesis				
7533	3	2	1		Other specified anomalies of kidney	1	1		

Appendix Table 1 (Cont'd)

ANALYZED RANCH HAND

SEVERE

ICD CODE	PRE-SEA				NOMENCLATURE	POST-SEA			
	Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable		Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable
7534	1	1			Other specified anomalies of ureter				
7539	3	1		2	Unspecified anomaly of urinary system	1	1		
75461	1	1			Congenital pes planus				
75470	2			2	Deformity foot, NOS, clubfoot	2	2		
75479	1			1	Other deformity of foot				
75529	1			1	Longitudinal deficiency phalanges				
75563	1	1			Other congenital deformity hip (joint)	1	1		
7560					Anomalies of skull & face bones	2	2		
75610	1			1	Anomaly of spine				
75615	1			1	Fusion of spine				
7580	1	1			Down's syndrome	2	2		
7591	1	1			Anomalies of adrenal gland				
7598	1	1			Other specified anomalies				
	50	32	2	16		34	30	2	2

Appendix Table 1 (Cont'd)

ANALYZED RANCH HAND

MODERATE

ICD CODE	PRE-SEA				NOMENCLATURE	POST-SEA			
	Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable		Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable
22800	2	1		1	Hemangioma, unspecified site				
5531	3			3	Umbilical hernia				
7438	3	1		2	Other specified anomalies of the eye				
74400	1	1			Unspecified anomaly ear with hearing impairment				
74421	1	1			Absence of the ear lobe	1		1	
74429					Other anomalies of the ear	1			1
7443					Unspecified anomaly of the ear	1		1	
7508					Other specified anomalies, upper alimentary tract	1	1		
75249					Other anomalies, female genitalia	1			1
7525	2			2	Undescended testicle				
7526	1			1	Hypospadias	2	2		
7531					Cystic kidney disease	1	1		
7538	1	1			Other specified anomalies of bladder and urethra				
7540	1		1		Musculoskeletal deformity, skull, face, jaw				
7542	3	2		1	Musculoskeletal deformity, spine				
75430					Dislocation, hip, unilateral	1	1		
75450	1	1			Talipes varus				
75453					Metatarsus varus	1	1		
75461	1	1			Pes planus				
75470	2			2	Deformity of foot, NOS				
75481	1	1			Pectus excavatum				
75489					Other specified, nonterato- genic anomalies	1	1		
75501					Polydactyly, fingers	1	1		
75502	1			1	Polydactyly of toes				
75513					Syndactyly, toes without fusion	1	1		
75563	3	3			Deformity of hip (joint)				
75566	2			2	Other anomalies of the toes				
75567	1			1	Other anomalies of the foot, NEC				
75569					Other anomalies of the lower limb	3	1	1	1

Appendix Table 1 (Cont'd)

ANALYZED RANCH HAND

MODERATE

ICD CODE	PRE-SEA				NOMENCLATURE	POST-SEA			
	Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable		Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable
7560	1			1	Anomalies of the skull & face bones				
75689	1	1			Other anomalies, muscle, tendons, fascia, connective tissue				
7569					Other & unspecified anomalies musculoskeletal system	1	1		
75733					Pigmentary anomalies of the skin	2	2		
7575					Specified anomalies of the nails	1		1	
	32	14	1	17		20	13	4	3

Appendix Table 1* (Cont'd)

ANALYZED RANCH HAND

LIMITED

ICD CODE	PRE-SEA				NOMENCLATURE	POST-SEA			
	Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable		Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable
2169	1	1			Benign neoplasm, skin, site unspecified				
7438					Other specified anomaly of eye	1	1		
74361					Ptosis	1	1		
74689	1			1	Other specified anomalies of heart				
7476					Other anomalies, peripheral vascular system	1		1	
7500	1			1	Tongue tie	2	2		
75010					Anomaly of tongue unspecified	1			1
75019					Other anomalies of tongue	1			1
75450					Talipes varus	3	2	1	
75460					Talipes valgus	1	1		
75470	1			1	Deformity feet NOS				
75479					Other specified deformity of feet	1	1		
75511					Syndactyly fingers without fusion	1			1
75513	1	1			Syndactyly toe with fusion				
75560	1			1	Unspecified anomaly lower limb	1			1

Appendix Table 1 (Cont'd)

ANALYZED RANCH HAND

LIMITED

ICD CODE	PRE-SEA				NOMENCLATURE	POST-SEA			
	Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable		Re- ported	Veri- fied	Not Sup- ported	Not Veri- fiable
75567					Anomalies of foot, NEC	1			1
75569					Other specified anomaly lower limb	1			1
75732					Hamartomas	5	2	1	2
75733					Pigmentary anomalies of skin	2	1		1
75739	1			1	Other specified anomalies, skin	2	1		1
7576	1			1	Other specified anomalies breast	1		1	
	8	2	0	6		26	12	4	10

Appendix Table 2

VERIFIED BIRTH DEFECTIVE CHILDREN
 WITHIN THE DEFINITION BY VERIFICATION OUTCOME, GROUP, TIME

<u>Group</u>	<u>Pre-SEA (%)</u>		<u>Post-SEA (%)</u>	
	<u>Yes</u>	<u>No</u>	<u>Yes</u>	<u>No</u>
Ranch Hand	47 (2.8)	1630 (97.2)	56 (6.3)	838 (93.7)
All Comparisons	73 (3.7)	1922 (96.3)	58 (4.5)	1218 (95.5)

Appendix Table 3
 VERIFIED BIRTH DEFECTIVE CHILDREN
 BY GROUP OCCUPATION AND TIME
 (All Comparisons)

<u>Occupation</u>	<u>Group*</u>	<u>Pre-SEA (%)</u>		<u>Post-SEA (%)</u>	
		<u>Yes</u>	<u>No</u>	<u>Yes</u>	<u>No</u>
Officer	RH	24 (3.0)	774 (97.0)	9 (3.9)	221 (96.1)
	AC	36 (3.8)	911 (96.2)	18 (4.5)	378 (95.5)
Fly Enl	RH	6 (1.7)	345 (98.3)	9 (8.7)	95 (91.3)
	AC	14 (3.5)	390 (96.5)	8 (5.9)	128 (94.1)
Gnd Enl	RH	17 (3.2)	511 (96.8)	38 (6.8)	522 (93.2)
	AC	23 (3.6)	621 (96.4)	32 (4.3)	722 (95.7)

(*RH = Ranch Hand, AC = All Comparisons)

Appendix Table 4

VERIFIED BIRTH DEFECTIVE CHILDREN
BY GROUP, TIME OF CONCEPTION AND VERIFICATION OUTCOME,
WITH BOTH PARENTS UNDER 35 AT CONCEPTION AND
MOTHERS WHO DID NOT DRINK ALCOHOL DURING PREGNANCY

A. Mothers not smoking during pregnancy.

<u>Group</u>	<u>Pre-SEA (%)</u>		<u>Post-SEA (%)</u>	
	<u>Yes</u>	<u>No</u>	<u>Yes</u>	<u>No</u>
Ranch Hand	25 (3.0)	818 (97.0)	28 (5.4)	493 (94.6)
All Comparisons	39 (3.5)	1061 (96.5)	37 (5.2)	676 (94.8)

B. Mothers smoking during pregnancy.

<u>Group</u>	<u>Pre-SEA (%)</u>		<u>Post-SEA (%)</u>	
	<u>Yes</u>	<u>No</u>	<u>Yes</u>	<u>No</u>
Ranch Hand	12 (3.1)	379 (96.9)	11 (8.1)	125 (91.9)
All Comparisons	22 (5.6)	371 (94.4)	8 (4.4)	173 (95.6)

Appendix Table 5

VERIFIED DEFECTIVE CHILDREN
BY SEVERITY, GROUP AND TIME OF CONCEPTION

<u>Time</u>	<u>Group</u>	<u>Not Defective</u>	<u>Defective (%)</u>		
			<u>Light</u>	<u>Moderate</u>	<u>Severe</u>
Post-SEA	RH	838	12 (21.4)	14 (25.0)	30 (53.6)
	AC	1218	9 (15.5)	24 (41.4)	25 (43.1)
Pre-SEA	RH	1630	2 (4.3)	13 (27.7)	32 (68.1)
	AC	1922	3 (4.1)	23 (31.5)	47 (64.4)

Appendix Table 6
 VERIFIED NEONATAL DEATHS
 BY TIME AND GROUP

<u>Group</u>	<u>Pre-SEA (%)</u>		<u>Post-SEA (%)</u>	
	<u>Yes</u>	<u>No</u>	<u>Yes</u>	<u>No</u>
Ranch Hand	18 (1.0)	1705 (99.0)	12 (1.3)	905 (98.7)
All Comparisons	23 (1.1)	2019 (98.9)	2 (0.2)	1307 (99.8)

REFERENCE

Newcombe and Tavendale. "Effects of Father's Age on the Risk of Child Handicap or Death," American Journal of Human Genetics, Vol 17: 163-178, 1965.